RESPONSE

Claims Rejection under 35 U.S.C. §112, second paragraph

Claims 30 and 31 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to distinctly point out the claimed subject matter. The Applicants have amended claim 30 in accordance with the Examiner's helpful suggestions to overcome this rejection.

With respect to the rejection of claim 31, the Examiner objected to use of the Markush format with a group of only two members, and suggested an appropriate amendment to overcome the rejection of claim 31. In accordance with the Examiner's suggestion, the Applicants presently remove the Markush group format from claim 31. However, in order to preserve the original intent of the Markush language, the Applicants have amended claim 31 to recite "ASIC cationic channels having the amino acid sequence of SEQ ID N0:2 ***or*** SEQ ID N0:8," as opposed to the suggested "SEQ ID N0:2 ***and*** SEQ ID N0:8." The Applicants believe that this amendment is in agreement with the intent of Examiner's suggestion. Accordingly, removal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

Claims Rejection under 3.5 U.S.C. §101

Claims 1, 11-13, 15, 17-23, 26-27, and 30-31 remain rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a credible, specific, or substantial utility. The Office Action alleges that Applicants did not provide disclosure regarding the function of the ASIC channel, nor any disease states associated with channel dysfunction. More specifically, the Office Action contends that the utility requirement is not

satisfied because the specification allegedly fails to establish a nexus between the ASIC channels and disease states of pain and neurodegeneration.

The Applicants respectfully disagree. The specification specifically discloses that the connection between ASIC channels and ischemic pain and neurodegeneration is through the induction of channel activity and the resulting ion influx. A role in the pain and neurodegeneration pathways imparts both a specific and substantial utility to the claimed channel; for example, for use as a drug screen for therapeutic compounds active against these particular diseases. The Applicants have also presented supporting data in the specification, discussed relevant knowledge in the prior art, and have identified post-filing publications that describe and confirm the relationship between ASIC channels and disease states. The Applicants assert that this evidence of record is probative of the asserted utility and therefore supports the credibility of the asserted utility.

With respect to the utility related to neurodegeneration, the Applicants maintain that one skilled in the art in view of the experimental data, specification, and knowledge in the art would be convinced that the activation of the claimed channels in the brain is involved in neurodegeneration. The literature at the time of filing indicates that brain ischemia is associated with brain acidosis at pH 6.5 and can aggravate brain injury as pH decreases (Siesjo *et al.* 1996. Adv Neurol. 71: 209-236). The Applicants have demonstrated that the ASIC channels are expressed in the brain and do exhibit activity at pH 6.5 (See Figs. 7 and 5b of Applicant's specification). Furthermore, Ca^{2+} influx is known to play a role in neurodegeneration, and the Applicants' data shows that the claimed channel is Ca^{2+} permeable (See Applicant's specification Fig. 5e and Choi. 1995. Trends Neurosci. 18 (2): 58-60). The *C. elegans* model of neurodegeneration shows that hyperactivity of several

homologs of the claimed channel results in cell death and, thereby, further supports the asserted relationship (See Driscoll *et al.* 1991. Nature. 349: 588-593, Chalfie *et al.* 1993. Nature. 361 (6412): 504, Chalfie *et al.* 1990. Nature. 345 (6274): 410-416, See also page 2, line 27 of the Applicants' specification). It was also known at the time of filing, that ASIC2a (MDEG) hyperactivity leads to cell death in mammals (See Waldmann *et al.* 1996. J Biol Chem. 271 (18): 10433-10436). The demonstrated relationship between brain acidosis, channel hyperactivity, calcium influx, and cell death is the nexus that connects the channels to neurodegeneration.

The Office Action argues, however, that a publication by Berdiev et al. suggests that data presented in the specification does not positively support the assertion that the ASIC channels are responsible for ischemic neurodegeneration in the brain. Specifically Berdiev et al. allegedly suggests that electrophysiological properties do not indicate a particular function of a channel and therefore the electrophysiological data related to amiloride-sensitivity does not support the asserted utility.

The Applicants maintain that Berdiev et al., which focuses on abnormal glioblastoma cells, is not relevant to the present claims. Indeed, the assertion that ASIC channels are expressed in glioma and glioma cell lines in Berdiev et al. is not consistent with the published literature. Figure 2 of Chen et al. indicates that neither ASIC1 nor ASIC3 are expressed in a glioma cell lines and Figure 2 of Waldmann et al. indicates that ASIC2 is not expressed in glial cells (See Chen *et al.* 1998. Proc Natl Acad Sci U S A. 95 (17): 10240-10245, and Waldmann *et al.* 1996. J Biol Chem. 271 (18): 10433-10436).

Therefore, as the Applicants have previously stated, Berdiev et al. is irrelevant to determining the role of ASICs in the normal brain cells because the present application

pertains to only normal, untransformed brain cells. Similarly, the Office Action arguments based on data from glioblastoma cells are irrelevant to ischemic pain.

The Office Action further cites the following statement of the publication by Berdiev et al. in further arguments regarding the credibility of the asserted utility.

> "amiloride-sensitive sodium channels cannot easily be classified based on simple biophysical parameters, such as single channel conductance and/or sensitivity to amiloride."

The Applicants assert that the above statement is incorrect. The neuronal ASIC channels described in the specification have properties that are different from their homologues, the epithelial sodium channel subunits (See ENaChs, See Rossier *et al.* 2002. Annu Rev Physiol. 64: 877-897). Indeed, the ASIC channels and the *C. elegans* degenerins are a distinct branch in the phylogenetic tree that is separate from the epithelial sodium channel subunits. (See Applicants' Specification, Figure 3). Furthermore, the epithelial sodium channels are blocked by amiloride concentrations that are about two orders of magnitude lower than those required to block ASIC channels (Applicants specification, pg. 18, ln. 23; Figure 6 d, e). Epithelial amiloride sensitive sodium channels, unlike ASICs, are constitutively active, are not activated by extracellular acid, and are not expressed in neurons. Thus, both biophysical properties and pharmacology allow classification of the different members of this ion channel family.

The Applicants further disagree with the assertion that amiloride sensitivity is not indicative of a role in pain sensation, and that the specification provides no significance of the function of amiloride as it correlates to the role of ASIC in pain sensation.

Acids have long been known to cause severe pain when applied to skin lesions or mucous membrane (See Keele and Armstrong. Substances Producing Pain and Itch. Barcroft, H., Davson, H., and Paton, W. D. M. [12]. 1964. London, Edward Arnold. Monographs of the

Physiological Society.). Pronounced acidification accompanies inflammation or ischemia where the local pH drops to values as low as 5.4 (See Häbler 1929 Klin.Wochenschrift 8, 1569-1572. 1929; Jacobus et al. 1977, Nature 265, 756-758.). Acidosis is also sufficient to provoke pain since intracutaneous injection of acid into human volunteers provoked pain (See Steen *et al.* 1993. Neurosci Lett. 154 (1-2): 113-116). Thus, tissue acidosis is well-known to be a mediator of pain.

At the time of filing, it was common textbook knowledge, that the control of discharge and, thus, pain signaling of nociceptive ("pain sensing") neurons depends ultimately on the activity of membrane ion channels. Thus, Na^+ or Ca^{2+} permeable ion channels in sensory neurons that are directly activated by extracellular acid or other pain mediators are highly interesting targets for the development of analgesic drugs.

A Na^+ permeable, **amiloride-blockable** ion channel that is activated by extracellular acid was described in 1981 in sensory neurons (See Krishtal *et al.* 1981. Neuroscience. 6 (12): 2599-2601; ref. 3 in the applicants specification). It was evident that such amiloride-sensitive H^+-gated cation channels in sensory neurons play a role in pain perception during tissue acidosis (See Bevan *et al.* 1991. J Physiol. 433: 145-161; ref. 24 in the Applicants' specification).

The specification establishes that ASIC mRNA is expressed in small pain sensing neurons of the dorsal root ganglion (Applicants' specification, pg. 19, ln. 19, Figure 8). Furthermore, contact of the claimed channels with acid induces an inflowing current with similar electrophysiological properties (inactivation kinetics, acid sensitivity, ionic selectivity, single channel conductance) to proton activated cationic channels of sensory neurons (Applicants' specification, pg. 17, ln. 24 ff, Figures 5 and 6)

The specification further shows that amiloride inhibits the inflowing current though

ASIC channels caused by protons (Applicants specification, pg. 18, ln. 23; Figure 6 d, e). The pharmacological properties of a cloned ion channel are commonly used to verify that the identity of a cloned channel is the same as the native ion channel. Thus, the fact that both the ASIC channels and the native acid-activated cation channels in sensory neurons are blocked by amiloride strongly suggests that ASIC channels are the acid sensors in sensory neurons.

In light of the foregoing, one skilled in the art would reasonably believe from the specification that ASIC channels are the acid activated amiloride sensitive cation channels described in sensory neurons. One skilled in the art would also accept that contact with acid activates the proton sensitive ASICs in the sensory neuron, which in turn causes an ion flux that results in an action potential that is interpreted as nociceptive pain. Indeed, two post filing publication further confirm that amiloride-sensitive acid sensing ion channels are responsible for the sensation of acid-induced pain in both human and mouse nociceptors (See Ugawa et al. 2002. J Clin Invest. 110(8):1185-1190 and Sluka *et al.* 2003. Pain. 106 (3): 229-239).

The Applicants assert that arguments presented above sufficiently describe the nexus between the claimed channels and the asserted disease states, and thus, verifies a credible, substantial, specific utility. However, the Office Action proposes several arguments that question the relationship between ASICs and neurodegeneration and pain, as asserted above, in the specification, and previous Office Action responses.

For example, the Office Action argues that the asserted function is based solely on the homology of the claimed channels to other known channels and, in accordance with *Brenner v, Manson,* similar structure does not indicate a shared function. The Office Action further suggests that the varied functions of members of the channel family are

sufficient reason to question the asserted utility.

However, homology is only one part of the body of evidence that supports the asserted utility. Indeed, the Applicants support their assertions of utility with expression studies and electrophysiological analysis of the claimed channel. The assertion of similar function and the associated utility is also supported by the combination of sequence homology data with the demonstrated similar electrophysiological properties (e.g. activation by extracellular acid, inactivation kinetics). Sequence homology, pharmacology and electrophysiological properties are each suggestive of a function, but when considered in combination with the entirety of the data in the specification and knowledge in the art, these features are at least probative of the asserted utility. Therefore, even if other members of the channel family have different biological functions, the combination of homology with the experimental data in the specification would reasonably convince one skilled in the art of the asserted utility.

The Office Action also alleges that the specification does not provide guidance as to whether activating the claimed channels would increase or decrease neurodegeneration (page 5, line 23 of the Office Action). The Applicants point to page 2, line 27 of the specification, which indicates that active mutants of MDEG (ASIC2a) channels are involved in neurodegeneration. Additionally, on page 9, line 1 of the specification, the Applicants state that screenings will allow the search for ASIC channel blockers that inhibit neurodegeneration. Thus, the Applicants' specification states that activating the channels leads to neurodegeneration and blocking ASIC channels would decrease neurodegeneration.

The Office Action also alleges that, in the absence of analysis of over or under expression of the claimed channel, one skilled in the art cannot determine the role of the

claimed channel in a disease state. The Office Action also states that the specification must connect the over or under expression of ASIC channels with a disease in order to use the invention to treat an associated disease. However, in the asserted disease states of acid-induced pain and neurodegeneration, it is the activation of the channels in response to acid, and not the degree of expression, which is responsible for its pathogenicity. Thus the on-off state of the channel controls a disease state, which confirms the utility of the invention without the need to associate pathology with over or under expression.

In additional arguments against the credibility of the asserted utility, the Office Action suggests that the role of the channel in neurodegeneration cannot be verified because the normal physiological role of ASIC in the brain has yet to be determined. To the contrary, the Applicants assert that knowledge of the normal physiological role of a protein has been accepted in the art as unnecessary for assessing its involvement in a disease pathway. For example, beta-amyloid is commonly understood to contribute to the pathology of Alzheimer's Disease and misfolded prion proteins are the cause of Spongiform Encephalopathy (BSE) in cattle or Creutzfeld Jakob disease in humans, despite the fact that non-pathogenic the roles of both beta-amyloid and prion proteins are unknown. The Applicants have provided evidence that the acid-induced hyperactivity of claimed channels is involved in neurodegeneration; therefore, the involvement of the channels in neurodegeneration would reasonably be accepted by one skilled in the art.

For the reasons presented above, the Applicant asserts that the specification provides sufficient evidence for one skilled in the art to accept the role of ASICs in the identified disease pathways and the associated asserted utility. As support of the credibility of the asserted utility, the Applicants point to the over 300 journal articles that cite the

underlying research of the present application (See Waldmann *et al.* 1997. Nature. 386 (6621): 173-177). These articles, especially the number that focus on neurodegeneration and pain, are a convincing indication that those skilled in the art have indeed accepted that the claimed channels are directly connected to the asserted disease states. Furthermore, the magnitude of citations demonstrates that the research underlying the present application was not only accepted by those skilled in the art, but also provided guidance for further research. If, as the Office Action alleges, the Applicant's data was not probative or convincing of a role in pain or neurodegeneration, other scientists would not have pursued further research into the role of ASICs in pain and neurodegeneration. As the specification and the frequently cited research contains the exact same data and conclusions regarding the role of ASICs in disease pathways, many individuals skilled in the art have indeed understood and accepted the asserted utility.

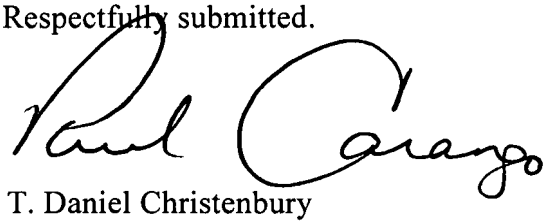
As the asserted roles in neurodegeneration and pain impart specific and substantial utility to the claimed channels, it is believed that the rejection under 35 U.S.C. § 101 rests largely on the credibility of the involvement the claimed channels in these disease states. The Applicants assert that the combination of the expression and electrophysiological data in the specification, homology to channels of known function, and common prior knowledge in the art is at least probative that the claimed channels are involved in ischemic pain and neurodegeneration. As credibility requirement is assessed by what one skilled in the art would accept as probative of the asserted utility, the Applicants assert the specification as filed satisfies the utility requirement. Furthermore, the numerous post-filing publications that cite the present study confirm the credibility of the asserted function and utility. Consequently, one skilled in the art would consider the asserted utility to be credible, and therefore the

utility requirement is satisfied. Accordingly, removal of the rejection under 35 U.S.C. § 101 is respectfully requested.

Claims Rejection under 35 U.S.C. 112, first paragraph

Claims 1, 11-13, 15, 17-23, 26-27, and 30-31 remain rejected under 35 U.S.C. § 112, first paragraph. This rejection follows from and is dependent upon the §101 rejection discussed above. Specifically, one skilled in the art is allegedly not enabled to use the invention because the claimed invention is allegedly not supported by a credible, specific, or substantial utility. For the reasons set forth above, the application does, in fact, describe sufficient specific, substantial and credible utilities for the claimed isolated polynucleotide of the ASIC channel. One skilled in the art would therefore know how to make and use the claimed invention. The Applicants, therefore, respectfully request that the §112, first paragraph rejection of claims 1, 11-13, 15, 17-23, 26-27, and 30-31 be withdrawn.

Respectfully submitted.



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